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Evaluation of Cefotaxime and Desacetylcefotaxime Concentrations in Cord Blood after Intrapartum Prophylaxis with Cefotaxime▽

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Preterm premature rupture of the membranes is associated with a high risk of neonatal sepsis. An increase in the incidence of early-onset neonatal sepsis due to ampicillin-resistant *Escherichia coli* in premature infants has been observed in the past few years. Intrapartum prophylaxis with ampicillin has proven to be efficient for the prevention of early neonatal sepsis due to group B streptococci. To date, there is no strategy for the prevention of early neonatal sepsis due to ampicillin-resistant *E. coli*. Our aim was to investigate whether a standardized dosage regimen of intrapartum cefotaxime could provide concentrations in the cord blood greater than the cefotaxime MIC_{90} for *E. coli*. Seven pregnant women hospitalized with preterm premature rupture of the membranes and colonized with ampicillin-resistant isolates of the family *Enterobacteriaceae* were included. Cefotaxime was given intravenously during delivery, as follows: 2 g at the onset of labor and then 1 g every 4 h until delivery. Blood specimens were collected from the mother 30 min after the first injection and just before the second injection, and at birth, blood specimens were simultaneously collected from the mother and the umbilical cord. The concentrations of cefotaxime in the cord blood ranged from 0.5 to 8.5 mg/liter. The MIC_{90} of cefotaxime for *E. coli* strains (0.125 mg/liter) was achieved in all cases. This preliminary study supports the use of cefotaxime for intrapartum prophylaxis in women colonized with ampicillin-resistant isolates of *Enterobacteriaceae*. The effectiveness of this regimen for the prevention of neonatal sepsis needs to be evaluated with a larger population.

Preterm premature rupture of the membranes (PPROM) occurs in 2.0 to 3.5% of pregnancies and results in preterm birth in 30 to 40% of cases (18). PPROM places the fetus at risk of premature delivery and the infant at risk of infection and the complications of prematurity. Infection has an important role either as a cause or as a consequence of PPROM (16).

Antibiotic treatment in pregnancies complicated by PPROM is associated with a delay in delivery and a reduction in the incidence of the major markers of neonatal morbidity and is now recommended in routine practice (12). However, there is concern that the increased use of antibiotics might result in a change in the bacteria isolated and their susceptibilities to antibiotics. This concern was supported by the previously described association between maternal antibiotic treatment and neonatal sepsis caused by bacteria resistant to the antibiotics administered to the mother (13, 20, 24, 25). An increase in the incidence of early-onset neonatal sepsis due to ampicillin-resistant *Escherichia coli* in premature infants has been observed in the past few years (10, 17, 20, 22). Infants with early-onset *E. coli* sepsis have poor outcomes: the mortality rate is 40% and a third of the survivors have been reported to manifest neurodevelopmental impairments (10). Furthermore, neonatal sepsis is an important cause of morbidity and death among infants with very low birth weights (21).

Although intrapartum prophylaxis with ampicillin has proven to be efficient for the prevention of early neonatal sepsis due to group B streptococci (19), to date, there is no strategy for the prevention of early neonatal sepsis due to ampicillin-resistant *E. coli*.

Cefotaxime has been shown to be active against a wide range of gram-positive and gram-negative organisms responsible for clinical infections like early neonatal sepsis, such as members of the family *Enterobacteriaceae* (mainly *E. coli*) and *Haemophilus influenzae*. Cefotaxime has a high degree of stability in the presence of the β-lactamases, both penicillinases and cephalosporinases, of gram-negative bacteria. As cefotaxime is safe for use during pregnancy (FDA category B), it might be efficient for the prevention of early neonatal sepsis due to ampicillin-resistant *Enterobacteriaceae*, mainly *E. coli*. The MIC_{90} of cefotaxime for *E. coli* strains is 0.125 mg/liter (14). Cefotaxime is metabolized into desacetylcefotaxime, which is also microbiologically active and which displays a MIC_{90} of 0.4 mg/liter for *E. coli* (11). As the efficacy of β-lactams is related to the time that the concentration in blood remains above the MIC ($T >$ MIC), it is important to know if efficient concentrations are achieved in fetal blood at delivery.

Only scarce data on the pharmacokinetics of cefotaxime in late pregnancy and during delivery exist. The placental transfer of a single intravenous dose of cefotaxime (1 g) has been evaluated in 11 pregnant women delivered at term by cesarean section. The results suggest that cefotaxime produces a sufficient clinical effect in perinatal infections, given the MIC of cefotaxime for the causative organisms (7). However, that study did not consider pregnancies complicated by PPROM, possibly making the results not relevant to preterm delivery following PPROM.

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TABLE 1. Main characteristics of the patients[a]

Patient no.	Prepregnancy BMI (kg/m^2)	GA at:		Length of PPROM (days)	Maternal vaginal culture result at inclusion	Highest maternal temp (°C) during delivery
		PPROM	Delivery			
1	25.7	33 wk	34 wk 6 days	13	*S. marcescens*	39.1
2	20.1	27 wk 4 days	35 wk 6 days	58	*E. coli*	36.1
3	20.7	29 wk 2 days	31 wk	14	*K. oxytoca*	38.8
4	22.2	31 wk 4 days	32 wk 2 days	5	*E. coli*	37.2
5	24.2	30 wk	32 wk 4 days	18	*K. pneumoniae*	36.8
6	18.6	29 wk 2 days	30 wk 4 days	9	*E. coli*	37.0
7	24.1	25 wk 4 days	35 wk	66	*E. coli*	37.4
8	26.9	32 wk 1 days	33 wk 2 days	8	*E. coli*	38.2

[a] Patient 3 was excluded from analysis as she did not receive cefotaxime. The MICs of cefotaxime were 0.125 mg/liter for *S. marcescens*, 0.01 to 0.06 mg/liter for *E. coli*, 0.03 mg/liter for *K. oxytoca*, and 0.06 mg/liter for *K. pneumoniae*. GA, gestational age.

The aim of this study was to use a standard regimen of intrapartum prophylaxis with cefotaxime and to evaluate if concentrations of cefotaxime and desacetylcefotaxime exceeding the MIC_{90} for *E. coli* can be obtained in cord blood at delivery.

MATERIALS AND METHODS

Pregnant women hospitalized with PPROM from January 2006 to May 2007 in two level 3 perinatal centers in Paris, France (Cochin-Saint Vincent de Paul and Port Royal Hospitals), were eligible for this prospective descriptive study. All women hospitalized with PPROM received amoxicillin (amoxicilline) at 3 g/day for 5 days according to local protocols. Vaginal swab specimens were taken at admission (i.e., before amoxicillin administration) and weekly, and no additional antibiotics were given. Screening for ampicillin-resistant *Enterobacteriaceae* is the standard of care in the Cochin-Saint Vincent de Paul Hospital for women hospitalized with PPROM. Women colonized with ampicillin-resistant *E. coli* or other ampicillin-resistant isolates of the *Enterobacteriaceae* were considered for inclusion in the study. Women who had multiple pregnancies, who had documented allergy to cefotaxime, or who had been treated with cefotaxime within 48 h before inclusion were excluded.

During labor, cefotaxime was given intravenously as follows: 2 g at the onset of labor and then 1 g every 4 h until delivery. Cefotaxime was dissolved in 50 ml 0.9% saline and was administered over 30 min. Blood specimens were collected from the mother 30 min after the first injection and just before the second injection, and at birth, blood specimens were simultaneously collected from the mother and the umbilical cord. At each time point, 5 ml of blood was drawn into evacuated collection tubes containing 85 IU lithium heparinate, and the tubes were labeled with sample identification information. All specimens were centrifuged (5,000 × *g*, 10 min) and stored at −20°C until analysis.

Demographic and clinical data were collected for each case. Maternal clinical data included age, prepregnancy body mass index (BMI), gestational age at PPROM and at delivery, length of PPROM, highest maternal temperature during delivery, and delivery route. Creatinine and C-reactive protein (CRP) concentrations were determined within 13 ± 6 h of delivery.

The clinical data collected for the infants included birth weight; umbilical cord blood pH; CRP concentration; the results of central (blood, cerebrospinal fluid), gastric aspirate, and peripheral (skin, ear) cultures; and complications during the neonatal period (respiratory distress syndrome, enterocolitis, intraventricular hemorrhage, leukomalacia, chronic lung disease, death). According to French recommendations, neonatal sepsis was defined as certain (positive blood or cerebrospinal fluid culture) or probable (negative blood and cerebrospinal fluid cultures, positive gastric and/or peripheral cultures, and/or clinical signs and/or increased CRP concentrations) (1). No molecular study was performed to determine if the organism isolated from an infant matched the organism from the infant's mother.

Cefotaxime and desacetylcefotaxime concentrations were determined by high-pressure liquid chromatography. Briefly, after addition of the internal standard (i.e., 50 μl of a 100-mg/ml cefazoline solution) to 50 μl of each plasma sample, the samples were precipitated with 250 μl of acetonitrile. The supernatants were evaporated at ambient temperature under a stream of nitrogen, and the dry residues were reconstituted with 250 μl of ammonium acetate buffer (0.05 M, pH 5). Fifty microliters of the extract was then injected into the chromatographic system, and separation was performed with a Cluzeau satisfaction C_{8+} column (250 by 3 mm; particle size, 5 μm) and a mobile phase consisting of a mixture of ammonium acetate buffer (0.05 M, pH 3)–acetonitrile–tetrahydrofuran (91.5:7.5:1, vol/vol/vol) at a flow rate of 0.5 ml/min. Detection was performed at a wavelength of 235 nm. The limit of quantification for both cefotaxime and desacetylcefotaxime was 0.1 mg/liter. The intra- and interday precisions and accuracies were less than 10% for both compounds over the calibration ranges (0.1 to 100 mg/liter for cefotaxime, 0.5 to 50 mg/liter for desacetylcefotaxime).

At birth, all infants received intravenous cefotaxime, amoxicillin, and gentamicin, according to French recommendations (1).

The study was approved by the Institutional Review Board of Cochin-Saint Vincent de Paul Hospital, and all women gave informed consent.

The results are expressed as the means ± standard deviations (ranges). A possible correlation between maternal clinical data (age, BMI, gestational age, length of PPROM) and cord cefotaxime concentration/mother cefotaxime concentration ratio was evaluated by linear regression.

RESULTS

Eight women were eligible for the study during the study period. The maternal BMI was 22.8 ± 2.9 kg/m^2 (range, 18.6 to 26.9 kg/m^2). The gestational age at the time of PPROM was 30 ± 2 weeks (range, 26 to 33 weeks). The gestational age at the time of delivery was 33 ± 2 weeks (range, 30 to 36 weeks), and the delay between the time of PPROM and the time of delivery was 24 ± 24 days (range, 5 to 66 days). The women were vaginally colonized with the following organisms at the time of inclusion: *E. coli* ($n = 5$), *Klebsiella oxytoca* ($n = 1$), *Klebsiella pneumoniae* ($n = 1$), and *Serratia marcescens* ($n = 1$); all these bacteria were ampicillin resistant (4) (Table 1). During labor, seven women received the standard regimen of cefotaxime. One woman (patient 3) did not receive cefotaxime and was excluded from the analysis. Five women received two doses of cefotaxime, and two were delivered before the second dose. The time that had elapsed between the time of the last administration of cefotaxime and the time of sampling was 116 ± 71 min (range, 15 to 225 min) (Table 2). No maternal adverse effect was reported.

The mean infant birth weight was 2,004 ± 631 g (range, 1,210 to 2,720 g). Four infants were colonized (i.e., they had positive peripheral cultures): one infant each with *S. marcescens*, *Pseudomonas aeruginosa*, group B streptococci, and *K. pneumoniae*. The organisms colonizing the infant matched the organism from the infant's mother in two cases (*S. marcescens* and *K. pneumoniae*), but molecular studies were not performed. Early-onset neonatal sepsis was suspected in two cases but was not confirmed. The neonatal course was uneventful in seven cases, and no adverse effect was reported. One infant had a late-onset neonatal sepsis during its hospitalization in

TABLE 2. Cefotaxime doses and concentrations in the mother and the umbilical cord blood[a]

Patient no.	Intrapartum			Delivery			Cord concn/mother concn ratio (%)
	No. of doses	Concn (mg/liter)		Concn (mg/liter)		Time (min) from last antibiotic administration to delivery	
		M30	Trough	Mother	Umbilical cord		
1	2	18.02	0.76	2.02	0.51	225	25
2	1	59.5	2.51	7.31	8.12	95	111
4	2	63.6	0.43	15.49	8.49	60	55
5	2	41.2	1.35	35.3	1.79	74	5
6	1	36.8	NA[b]	4.07	5.5	114	135
7	2	15.3	1.03	1.95	3.35	195	172
8	2	74.4	NA	1.99	0.72	15	36

[a] Blood specimens were collected from the mother 30 min after the first injection (M30) and just before the second injection (trough), and at birth, blood was simultaneously collected from the mother and the umbilical cord.
[b] NA, not available.

the neonatal intensive care unit due to a coagulase-negative staphylococcus.

Tables 2 and 3 summarize the results. The MIC_{90} of cefotaxime for the *E. coli* strains (i.e., 0.125 mg/liter) was achieved in all cases. The lowest concentration achieved in the cord blood (0.51 mg/liter) exceeded three times the MIC_{90}. The cefotaxime cord concentration/mother concentration ratios ranged from 5 to 172% (mean, 77%). The desacetylcefotaxime concentration in cord blood was at least seven times higher than its MIC_{90} for *E. coli* (i.e., 0.4 mg/liter), and the cord concentration/mother concentration ratios ranged from 31 to 187% (mean, 100%).

DISCUSSION

The results of the present study indicate that during preterm delivery following PPROM, a standard intrapartum prophylaxis with a cefotaxime dose of 2 g followed by a dose of 1 g every 4 h achieved cefotaxime and desacetylcefotaxime concentrations in cord blood greater than the cefotaxime MIC_{90} and the desacetylcefotaxime MIC_{90} for *E. coli* and other members of the family *Enterobacteriaceae*.

The placental transfer of cefotaxime has previously been measured in late pregnancy during delivery by cesarean section (7). That study demonstrated that the level of cefotaxime remained comparatively high in the cord blood 6 h after the administration of 1 g of cefotaxime to the mother. Because the gestational age at the time of delivery is lower after PPROM, the placental transfer of the drug after PPROM could be different from that at term delivery. Our results give information about the placental transfer of cefotaxime and desacetylcefotaxime during preterm delivery following PPROM and show that PPROM and preterm delivery do not alter the diffusion of cefotaxime or desacetylcefotaxime in the fetus. Our results are consistent with those of previous studies of cefuroxime that showed that the therapeutic concentrations of cefuroxime could be achieved in cord blood after treatment of the mother during PPROM (6) and in fetal blood during uncomplicated pregnancies (9).

TABLE 3. Desacetylcefotaxime concentrations in the mother and the umbilical cord blood[a]

Patient no.	Concn (mg/liter)				Cord concn/mother concn ratio (%)
	Intrapartum		Delivery		
	M30	Trough	Mother	Umbilical cord	
1	14.1	3.53	3.17	4.62	146
2	4.77	4.08	5.62	4.87	87
4	11.7	1.97	8.28	5.24	63
5	8.59	3.68	6.53	12.2	187
6	12.5	NA[b]	5.39	3.78	70
7	10.6	3.19	3.99	4.46	112
8	14.1	NA	10.2	3.15	31

[a] Blood specimens were collected from the mother 30 min after the first injection (M30) and just before the second injection (trough), and at birth, blood was simultaneously collected from the mother and the umbilical cord.
[b] NA, not available.

However, the cord concentration/mother concentration ratio varied greatly between women, making the cord blood concentration unable to be predicted on the basis of the level of maternal exposure. This ratio also depends on the differences between the pharmacokinetics of the drug in the mother and the pharmacokinetics of the drug in the fetus. The ratio was found to vary until the achievement of the pharmacokinetic steady state in the mother and the fetus (23). Our limited number of cases did not allow us to investigate precisely the placental transfer of the drug, as the number of doses administered, the time that had elapsed between the time of drug administration and the time of sampling, and the gestational age of the infants varied among the cases. No correlation between maternal clinical data and cord cefotaxime concentration/mother cefotaxime concentration ratio was found. However, our primary objective was not to determine precisely the placental transfer of cefotaxime during PPROM but to investigate if a standardized regimen could provide an efficient exposure to the fetus during delivery.

The two main factors that predict bacterial killing in vivo are the level of drug exposure achieved in an individual patient and the MIC of the antibacterial agent for the bacteria causing the infection. For β-lactams, $T > MIC$ is the best correlate of efficacy (2). As the $T > MIC$ increases from 33% to 50% of the dosing interval, the bacteriological cure rate reaches its maximum (15). The concentrations of cefotaxime and desacetylcefotaxime achieved in intrapartum samples were always above their respective MICs (MIC_{90} of cefotaxime, 0.125 mg/liter; MIC_{90} of desacetylcefotaxime, 0.4 mg/liter) (14). When the dosing interval is considered the interval between the time of administration of cefotaxime and the time of

delivery, the concentration of cefotaxime was above the MIC for at least 80% of the dosing interval (Table 2). This should therefore allow good bacterial killing, as recommended. It seems important to confirm our findings with a larger population to better characterize the pharmacokinetic variability of the placental transfer of cefotaxime and desacetylcefotaxime and, consequently, the probability that efficacious concentrations of these compounds are achieved in cord blood at delivery.

Even though the results of the present study may support the intrapartum use of cefotaxime for the prevention of neonatal sepsis due to ampicillin-resistant isolates of the *Enterobacteriaceae*, it is still unclear if achieving concentrations above the MIC in cord blood at delivery is the optimal pharmacological end point. A penultimate goal would have been to draw blood directly from the infant at different times after birth. For ethical reasons, this was not done in our study. Nevertheless, the drug concentration in cord blood is usually considered to reflect the concentration in the newborn (2).

The cefotaxime concentration in cord blood at delivery does not take into account the possible need for prolonged prophylactic treatment of the infant. A previous pharmacokinetic study performed with premature infants found a cefotaxime elimination half-life of 3.68 ± 1.48 h (5). Thus, according to the cefotaxime concentrations observed in cord blood, it seems that cefotaxime will remain above the MIC for only a few hours in some infants. Further studies are therefore needed to determine if treatment of the infants could provide some supplemental benefit against the risk of neonatal sepsis in this context. Lastly, the women included in the study had normal BMIs, and our results cannot necessarily be generalized to obese women.

The administration of ampicillin for the prevention of group B streptococcal infection was found to exert pressure that resulted in an increase in the incidence of ampicillin-resistant *Enterobacteriaceae*, and one cannot exclude the possibility that the administration of cefotaxime to pregnant women colonized with ampicillin-resistant *Enterobacteriaceae* might exert pressure that results in the production of extended-spectrum beta-lactamases or cefotaxime resistance (3).

In conclusion, this preliminary study shows that in pregnant women colonized with ampicillin-resistant isolates of the family *Enterobacteriaceae*, prophylactic treatment with cefotaxime during delivery could provide concentrations of cefotaxime and desacetylcefotaxime above the MIC in fetal blood at delivery. Studies with larger populations are needed to evaluate the effectiveness of this prophylactic strategy for the prevention of early-onset neonatal sepsis due to ampicillin-resistant *Enterobacteriaceae*.

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